Is Melatonin Protective in Contrast Material Related Renal Failure?

Melatonin Kontrast Madde İle İlişkili Renal Yetmezlikten Korur mu?

Melatonin Böbrek Yetmezliğinden Korur mu? / Is Melatonin Protect from Renal Failure?

Ozum Tuncyurek[1], Ozlem Gunay[2], Fatma Taneli[3], Semin Ayhan[4], Nalan Nese[4], Yuksel Pabuscu[5]
[1]Aydin Ataturk Goverment Hospital, Radiology Dep, Aydin, [2]Biolab Laboratory Groups, Biochemistry Dep, Izmir,
[3]Celal Bayar University Faculty of Medicine, Biochemistry Dep, Manisa, [4]Celal Bayar University Faculty of Medicine, Pathology Dep, Manisa,
[5]Celal Bayar University Faculty of Medicine, Radiology Dep, Manisa, Turkey

Özet

Amaç: Çalışmanın amacı, erkek sıçanlarda myoglobinüri ve radyokontrast maddeye bağlı oluşan böbrekyetmezliğinde melatoninin etkisini araştırmaktır. Gereç ve Yöntem: Anestezi eşliğinde,tüm sıçanların her iki arka bacağına eşit miktarda %50'lik gliserol uygulanarak myoglobinürik böbrekyetmezliği geliştirildi. 3 saatsonra :Grup I (n:7): Iopromide (Ultravist-300®) 2 ml/kg (intrakardiak); Grup II (n:7): Iopromide(Ultravist -300®)ve intraperitoneal olarak Melatonin (10 mg/kg) ; Grup III (n:7): 2 ml/kg fizyolojik salin (Kontrolgrubu). Kan örnekleri toplanarak üre, kreatinin ve cystatin c değerleri çalışıldı. Protokolü bilmeyen iki patolog tarafından böbrekler incelendi. Bulgular: Grup 2 ile 3 arasında kreatinin ve cystatin c değerleriiçinfarkyoktu (p=0.9; 0.2). Tartışma: Çalışmada, kontrasta bağımlı böbrekte oluşan oksidatif stresin melatonin ile önlenebildiğini gösterdik. Ancak, insanlar damelatoninin koruyucu etkilerinin ekklinik çalışmalarla değerlendirilmesine ihtiyaç vardır.

Anahtar Kelimeler

Akut Böbrek Yetmezliği; Kontrast Bağımlı Nefrotoksisite; Lopromide Melatonin

Abstract

Aim: The aim of the study was to investigate the effect of melatonin on the renal injury resulting from radiocontrast media and myoglobinuria in male Wistar albino rats. Material and Method: 50% glycerol at equal amounts was intramuscularly administered to both hind legs of all animals under ether anesthesia at the dose of 10 mg/kg. Three hours later, the groups were administered the following: Group I (number:7): Iopromide(Ultravist -300®) at the dose of 2 ml/kg (intracardiac); Group II (number:7): Iopromide(Ultravist -300®) and intraperitoneally administered Melatonin at the dose of 10 mg/kg (Melatonin was dissolved in 7.5% absolute ethanol and further dilutions were made in saline.); and Group III (number:7): 2 ml/kg of sterile physiologic saline (Control group). The levels of Uurea, Ccreatinine and Ccystatin C were studied on the blood samples collected. The renal samples were evaluated by 2two distinct pathologists who did not know the protocol. Results: There was no difference in the values of Creatinine and cystatin c between Groups 2 and 3 (p=0.9; 0.2). Discussion: In conclusion, we evaluated the possible prevention of contrast-induced oxidative stress in the kidney with using melatonin. However, additional clinical studies are needed to evaluate the role of preventive melatonin treatment in humans.

Keywords

Acute Renal Failure; Contrast Induced Nephrotoxicity; Lopromide Media Melatonin

DOI: 10.4328/JCAM.1929 Received: 03.06.2013 Accepted: 27.06.2013 Printed: 01.03.2015 J Clin Anal Med 2015;6(2): 186-9
Corresponding Author: Özüm Tunçyürek, Aydin Atatürk Devlet Hastanesi, Radyoloji Ultrason Bölümü, 09010 Aydin, Türkiye.
GSM: +905301437669 F.: +90 2562252505 E-Mail: ozum.tuncyurek@gmail.com

Introduction

Contrast media are medicines which are frequently used in imaging examinations (1). However, their use is limited by their nephrotoxicity, with about 30–50% (2) of intensive care unit patients experiencing a significant decline in renal function after a single dose of radiocontrast agents.

The 3rd most frequent cause of the inpatient acute renal failure (ARF) is the contrast-induced nephropathy (3). An alteration in renal hemodynamics plays a central role in the pathophysiology of CIN (contrast ınduced nephrotoxicity (CIN). In an effort to reverse these hemodynamic changes, vasodilators and diuretics have been tested as prophylactic drugs (4).

The mechanism of Contrast-induced nephrotoxicity (CIN) is not completely understood; however, the most frequent causes include renal medullar ischemia resulting from contrast-induced vasoconstriction and the direct toxic effect of contrast agents on renal tubular cells. While the type of contrast media, ions, concentration and hypoxia play the most important role in cellular injury, it is reported in the literature that osmolality plays a secondary role (5, 6).

Acute Renal Failure (ARF) is a clinical syndrome characterized by rapid deterioration of renal function and it is estimated to occur in at least 5% of all hospitalized patients, and in 30–50% of those admitted to the intensive care unit (1, 7). Contrast-induced nephropathy (CIN) is defined as ARF occurring within 48 h of exposure to an intravascular contrast medium (8). The use of contrast media in the procedures of diagnostic and interventional radiology is on the increase.

The CIN ranks third among the causes of hospital-acquired ARF. The selection of new and reliable contrast media becomes essential (4).

Melatonin (N-acetyl-5-methoxytriptamine) is synthesized and released into the circulation and especially into the cerebrospinal fluid by the pineal gland in a circadian rhythm (9) and it is also produced by the immune system cells, brain, airway epithelium, bone marrow, gut, ovary, testes, skin, and other likely tissues (10). Melatonin and its metabolites possess free radical scavenging activities (11). Melatonin has both receptor-mediated and receptor-independent actions and is believed to affect all cells (12, 13).

Melatonin increases mRNA and protein levels of antioxidant enzymes. Based on these findings, we hypothesized that melatonin might exert beneficial effects and prevented renal injury when administered for clinical conditions associated with ARF. In the present study, we evaluated the effect of systemically administered melatonin on well-established animal models of contrast medium-induced renal dysfunction and tubular injury.

Material and Method

This study was carried out in the laboratory of the Scientific Field of Experimental Surgery and Research in the Faculty of Medicine at Ege University. 4 to 6-month-old male Wistar Albino rats, weighing 150-200 g and obtained from the Animal Production Center affiliated to the Scientific Field of Experimental Surgery and Research, were used in the study. All subjects were treated according to their sizes with the permission by the ethics committee. Totally 21 rats were used in 3 groups in the study. All rats were weighed at the beginning of the experiment. Before the experiment, all groups had been deprived of water for 24 hours.

50% glycerol at equal amounts was intramuscularly administered to both hind legs of all animals under ether anesthesia at the dose of 10 mg/kg. Three hours later, the groups were administered the following: Group I (number:7): Iopromide(Ultravist-300®) at the dose of 2 ml/kg (intracardiac); Group II (number:7): Iopromide(Ultravist -300®) and intraperitoneally administered Melatonin at the dose of 10 mg/kg (Melatonin was dissolved in 7.5% absolute ethanol and further dilutions were made in saline.) and Group III (number:7): 2 ml/kg of sterile physiologic saline (Control group). Groups I, II, and III: 8 hours later, ketamine hydrochloride (Ketalar, Parke-Davies) at the dose of 10 mg/kg was administered intramuscularly, and anesthesia was applied. Padding was placed under the thoracic arch, and midline laparotomy was applied. It was continued with the retroperitoneal space, and bilateral nephrectomy was applied. 3-4 cc of arterial blood sample was collected with simultaneously transdiaphragmatic puncture into the heart.

The levels of urea, creatinine and cystatin c were studied on the blood samples collected. Urea and creatinine were studied by means of an Integra 800 (Roche Diagnostic-s,Germany) apparatus with the enzymatic method. Cystatin c was studied by means of a DNM-9602 Microplate Reader apparatus with the ELISA method and read at 320 nm.

The renal materials collected were divided into two parts in the longitudinal axis, placed into a 10% formaldehyde solution, and fixed. After they had been embedded in paraffin blocks, sections with a thickness of 3 to 5 microns were obtained from the blocks. Later on, they were stained with the Hematoxylin-eosin method, and the sections were evaluated by means of a light microscope. The histopathological evaluation was made by two different pathologists who did not know the medicine protocol. The accumulation of myoglobin in the tubule lumen and tubular necrosis were scored semiquantitatively and recorded . The criteria for scoring are shown in Table 2 and 3.

The statistical analysis of the differences was made with the SPSS 11.0 program; the differences in biochemical tests were analyzed with the analysis of variance; and the histological changes occurring in kidneys were analyzed with the Kruskal Wallis and Mann-Whitney U analysis.

Table 1. Biochemical Findings

	Group1	Group2	Group3
Urea (mg/dl)	125	73	33
Creatine (mg/dl)	1.1	0.5	0.3
Cystatine-C (mg/l)	2.7	0.3	0.3

Table 2. Median scores of Histological Findings

	Group1	Group2	Group3
Tubular necrosis	3	1.5	2
Myoglobine casts	2	1.5	0

Results

As shown in Table 1, the values of Plasma urea, creatinine and cystatin c were high in Group 1 in comparison with those in the other two groups (p= 0.009; 0.01; 0.003). There was a difference

Table 3. Score table *:

SCORE	Tubular necrosis	Myoglobin casts
0	No necrosis	No casts
1	Focal necrotic foci in less than 10% of the cortex and/or cytoplasmic granular changes in the accompanying tubular epithelial cells	Casts stained in brown in the eosinophilic or late phase in less than 5% of the cortical tubular lumens
2	Necrotic foci in 10-25% of the cortex and/or cytoplasmic granular changes in the accompanying tubular epithelial cells	Presence of myoglobin casts in 5-10% of the cortical tubules
3	Presence of necrotic foci in 25-50% of the cortex	Presence of myoglobin casts in 10-25% of the cortical tubules
4	Common necrosis involved in more than 50% of the cortex	Presence of common casts in the cortex and the medulla

* Ersin S, Zeybek A, Şen Sait, Akalın T, Akyıldız M. Proflactic effects of mannitol and furosemid in experimental acute renal failure İzmir Atatürk Eğitim Hastanesi Tıp Dergisi 37 (1-2):27-31,1999

in the values of Urea between Groups 2 and 3 (p=0.03), whereas there was no difference in the values of creatinine and cystatin c between Groups 2 and 3 (p=0.9; 0.2).

The histological changes in all the groups were graded, and the results are shown in Table 2.The histological findings most obviously occurred in Group 1. The cast score findings were significantly different from the control group (p=0.002) (Figure 1). There were no significant differences in the necrosis score between the groups (p=0.5).

Discussion

The pineal hormone melatonin plays a major role in the circadian sleep-wake rhythm. The present study provides the evidence that melatonin has therapeutic potential by attenuating renal injury in experimental animal models of ARF. Single intravenous administration of melatonin provided protection against glycerol-induced injury in rats, as evidenced by the biochemical as well as better histological profiles in the melatonin-treated kidneys. This can be assumed based on the fact that melatonin produced a relatively small, but significant, decrease in serum urea, creatinine and cystatin c levels as compared with animals subjected to glycerol-induced injury only.

CysC is produced at a constant rate by all nucleated cells. Under normal situations, it is freely filtered by the glomeruli and totally reabsorbed in the proximal tubule. In the absence of tubular dysfunction, its serum level reflects glomerular filtration and can be used as a functional marker for acute and chronic changes in GFR (12,13)

Melatonin and its metabolites force the antioxidant system to work through free radicals. An antioxidant enhances the synthesis of enzymes and increases the efficiency of other antioxidants (14).

Wang et al. showed that protection against cardiopulmonary bypass-induced renal injury could be ensured under the antioxidant effect of melatonin (15, 17).

Actually, there has been much evidence which shows that the CKD (chronic kidney disease) leads to oxidative stress (18, 19), which speeds up the progression of renal injury not only directly by causing cytotoxicity but also indirectly by developing inflammation (18-21).

As the literature demonstrates, the side effects of melatonin on humans are very few, and it reduces brain injury in mice and the ischemic stroke injuries in rats (16, 17).

The antioxidant characteristic of melatonin was shown in studies in the literature such as neurodegeneration, traumatic brain injury and antibiotic-induced renal injury in animal models (18, 19). In the last decade, in various models of acute and chronic tissue injury and oxidative stress, it was shown that the main mechanism for melatonin's protective effect was its action through indirect effects.

It has been recently shown in this experiment that melatonin has a protective function against the renal failure caused by glycerol and contrast media. Myoglobinuria-induced acute renal failure is among the frequently encountered ischemic cases (22, 23).

We used in this experiment Iopromide because of the low osmolarity contrast material characteristic (24)

Reperfusion, developing after ischemic cases, leads to an increase in injuries via reactive oxygen products. Oxidative stress in uremia takes place both due to the increased generation of reactive oxygen products and owing to the depletion of antioxidant defenses (25, 26). Of them, melatonin deficiency (27-29) might have a contribution to the decreasing of antioxidant capacity in renal failure. Thus, in their study, Quiroz et al. (30) tested the hypothesis that melatonin supplementation might retard the progression of renal disease by reducing oxidative stress and inflammation (31-33).

In this study, it was determined that melatonin reversed the radiocontrast-induced renal injury without any problems. The literature contains studies which support this information. Nevertheless, more clinical studies are required.

Conclusion

In conclusion, we evaluated the possible prevention of contrast induced oxidative stress in the kidney with melatonin usage. These data may have research hints of the therapeutic uses of melatonin. Melatonin may be beneficial to the prevention of contrast-induced nephrotoxicity.

However, additional clinical studies are needed to evaluate the role of preventive melatonin treatment in humans.

Competing interests

The authors declare that they have no competing interests.

References

1. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet 2005;365(9457):417-30.
2. Diamantopoulos A, Kyriazis I, Geronatsiou K, Papadaki H, Loudos G, Kagadis GC et al. Parstatin prevents renal injury following ischemia/reperfusion and radiocontrast administration. Am J Nephrol 2012;36(3):278-86.
3. Krasuski RA, Sketch Jr MH, Harrison JK. Contrast agents for cardiac angiography: osmolality and contrast complications. Curr Interv Cardiol Rep 2000;2(3):258-66.
4. Briguori C, Marenzi G. Contrast-induced nephropathy: pharmacological prophylaxis. Kidney Int Suppl 2006;(100):30-8.
5. Murphy SW, Barrett BJ, Parfrey PS. Contrast nephropathy. J Am Soc Nephrol 2000;11(1):177-82.
6. Murphy B, Rao QA, Newhouse JH. Contrast material-induced nephropathy. Radiology 2007;243(2):606
7. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis 2002;39(5):930-6.
8. Finn WF. The clinical and renal consequences of contrast-induced nephropathy. Nephrol Dial Transplant 2006;21(6):2-10.
9. Reiter RJ TD, Leon J, Kilic U, Kilic E. When melatonin gets on your nerves: its beneficial actions in experimental models of stroke. ExpBiol Med (Maywood) 2005;230:104–117
10. Reiter RJ, Paredes SD, Manchester LC, Tan DX. Reducing oxidative/nitrosative stress: a newly-discovered genre for melatonin. Crit Rev Biochem Mol Biol

2009;44(4):175-200.
11. Hardeland R, Tan DX, Reiter RJ. Kynuramines, metabolites of melatonin and other indoles: the resurrection of an almost forgotten class of biogenic amines. J Pineal Res 2009;47(2):109-26.
12. Soto K, Coelho S, Rodrigues B, Martins H, Frade F, Lopes S et al. Cystatin C as a marker of acute kidney injury in the emergency department. Clin J Am Soc Nephrol 2010;5(10):1745–54.
13. Perrin T, Descombes E, Cook S. Contrast-induced nephropathy in invasive cardiology. Swiss Med Wkly 2012; DOI: 10.4414/smw.2012.13608.
14. Kilic U, Yilmaz B, Ugur M, Yüksel A, Reiter RJ, Hermann DM et al. Evidence that membrane-bound G protein-coupled melatonin receptors MT1 and MT2 are not involved in the neuroprotective effects of melatonin in focal cerebral ischemia. J Pineal Res 2012;52(2):228-35.
15. Kilic U, Kilic E, Tuzcu Z, Tuzcu M, Ozercan IH, Yilmaz O et al. Melatonin suppresses cisplatin-induced nephrotoxicity via activation of Nrf-2/HO-1 pathway. Nutr Metab (Lond) 2013; DOI: 10.1186/1743-7075-10-7.
16. Tan DX, Manchester LC, Terron MP, Flores LJ, Reiter RJ. One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen and nitrogen species. J Pineal Res 2007;42(1):28-42.
17. Wang Z, Zhang J, Liu H, Huang H, Wang C, Shen Y et al. Melatonin, a potent regulator of hemeoxygenase-1, reduces cardiopulmonary bypass-induced renal damage in rats. J Pineal Res 2009;46(3):248-54.
18. Himmelfarb J. Linking oxidative stress and inflammation in kidney disease: which is the chicken and which is the egg. Semin Dial 2004;17(6):449-54.
19. Vaziri ND, Dicus M, Ho ND, Boroujerdi-Rad L, Sindhu RK. Oxidative stress and dysregulation of superoxide dismutase and NADPH oxidase in renal insufficiency. Kidney Int 2003;63(1):179-85.
20. Vaziri ND, Bai Y, Ni Z, Quiroz Y, Pandian R, Rodriguez-Iturbe B. Intra-renal angiotensin II/AT1 receptor, oxidative stress, inflammation, and progressive injury in renal mass reduction. J Pharmacol Exp Ther 2007;323(1):85-93.
21. Rodriguez-Iturbe B, Pons H, Herrera-Acosta J, Johnson RJ. Role of immunocompetent cells in nonimmune renal diseases. Kidney Int 2001;59(5):1626-40.
22. Chatzizisis YS, Misirli G, Hatzitolios AI, Giannoglou GD. The syndrome of rhabdomyolysis: complications and treatment. Eur J Intern Med 2008;19(8):568-74.
23. Funk JA, Schnellmann RG. Persistent disruption of mitochondrial homeostasis after acute kidney injury. Am J Physiol Renal Physiol 2012; DOI: 10.1152/ajprenal.00035.2011.
24. Lenhard DC, Pietsch H, Sieber MA, Ernst R, Lengsfeld P, Ellinghaus P et al. The osmolality of nonionic, iodinated contrast agents as an important factor for renal safety. Invest Radiol 2012;47(9):503-10.
25. Vaziri ND. Oxidative stress in uremia: nature, mechanisms, and potential consequences. Semin Nephrol 2004;24(5):469-73.
26. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. Kidney Int 2002;62(5):1524-38.
27. Parlakpinar H, Acet A, Gul M, Altinoz E, Esrefoglu M, Colak C. Protective effects of melatonin on renal failure in pinealectomized rats. Int J Urol 2007;14(8):743-8.
28. Vaziri ND, Oveisi F, Reyes GA, Zhou XJ. Dysregulation of melatonin metabolism in chronic renal insufficiency: role of erythropoietin-deficiency anemia. Kidney Int 1996;50(2):653-6.
29. Vaziri ND, Oveisi F, Wierszbiezki M, Shaw V, Sporty LD. Serum melatonin and 6-sulphatoxymelatonin in end-stage renal disease: Effect of hemodialysis. Artif Organs 1993;17(9):764–9.
30. Quiroz Y, Ferrebuz A, Romero F, Vaziri ND, Rodriguez-Iturbe B. Melatonin ameliorates oxidative stress, inflammation, proteinuria, and progression of renal damage in rats with renal mass reduction. Am J Physiol Renal Physiol 2008;294(2):336-44.
31. Pei Z, Pang SF, Cheung RT. Pretreatment with melatonin reduces volume of cerebral infarction in a rat middle cerebral artery occlusion stroke model. J Pineal Res 2002;32(3):168-72.
32. Sener G, Sehirli AO, Altunbas HZ, Ersoy Y, Paskaloglu K, Arbak S et al. Melatonin protects against gentamicin-induced nephrotoxicity in rats. J Pineal Res 2002;32(4):231-6.
33. Hara M, Yoshida M, Nishijima H, Yokosuka M, Iigo M, Ohtani-Kaneko R et al. Melatonin, a pineal secretory product with antioxidant properties, protects against cisplatin-induced nephrotoxicity in rats. J Pineal Res 2001;30(3):129-38.